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TITLE: Targeting trypsin-inflammation axis for pancreatitis therapy in a humanized pancreatitis model

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13. SUPPLEMENTARY NOTES					
14. ABSTRACT Acute pancreatitis especially due to alcohol and smoking goes onto chronic pancreatitis which, in turn, is a risk factor for pancreatic cancer. Because only a relatively small portion of patients with alcohol abuse and smoking develop pancreatitis, it is very likely that there are genetic underlying predisposing factors that have not been discovered that explain why certain individuals develop pancreatitis. A genetic defect in the trypsinogen gene (PRSS1 gene) causing hereditary pancreatitis is now well established. We developed a transgenic mouse using a Bacterial Artificial Chromosome harboring the full-length human PRSS1 with the key mutation of hereditary pancreatitis (PRSS1R122H). During the funding year we used this novel mouse model to determine whether PRSS1R122H and heavy drinking and smoking predispose to pancreatitis. Our data so far indicates that mice expressing PRSS1R122H develop a more severe form of pancreatitis than wild type mice and recovery after pancreatitis is impaired. We are working now in understanding the mechanisms underlying the observed effects.					
15. SUBJECT TERMS Pancreatitis, acute pancreatitis, chronic pancreatitis, hereditary pancreatitis, alcohol abuse, smoking, endoplasmic reticulum stress.					
16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT UU	18. NUMBER OF PAGES 10	19a. NAME OF RESPONSIBLE PERSON USAMRMC
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4. INTRODUCTION:

Pancreatitis is an inflammatory disease of the pancreas that causes significant morbidity and mortality. Pancreatitis occurs in acute and chronic variants. Acute pancreatitis especially due to alcohol and smoking goes onto chronic pancreatitis which, in turn, has the highest proportional risk for pancreatic cancer of any known environmental risk factor. Because only a relatively small portion of patients with alcohol abuse and smoking develop pancreatitis, it is very likely that there are genetic underlying predisposing factors that have not been discovered that explain why certain individuals develop pancreatitis. A genetic defect in the trypsinogen gene (PRSS1 gene) causing hereditary pancreatitis is now well established. We developed a transgenic mouse using a Bacterial Artificial Chromosome harboring the full-length human PRSS1 with the key mutation of hereditary pancreatitis (PRSS1^{R122H}). With this novel model, we will test our **central hypothesis** that physiological/environmental factors interact with PRSS1^{R122H} to activate the trypsin-endoplasmic reticulum (ER) stress- inflammation axis and cause both acute and chronic pancreatitis and progression to pancreatic cancer. Targeting the ER stress and inflammatory cascade will be beneficial for pancreatitis prevention and therapy. We expect that this study will elucidate fundamental mechanisms of pancreatitis and provide a preclinical platform for testing potential therapies.

5. KEYWORDS:

Pancreatitis, acute pancreatitis, chronic pancreatitis, hereditary pancreatitis, alcohol abuse, smoking, inflammation, cell death, endoplasmic reticulum stress.

6. ACCOMPLISHMENTS:

6.1. Major goals of the project (Cedars-Sinai Medical Center site):

The major goals described in the approved SOW remain the same.

Specific Aim 2: Determine the role of PRSS1^{R122H} and alcohol/smoking in the development of pancreatitis.

Subtask 1: Test the hypothesis that mutant PRSS1 expression cooperates with ethanol and smoke extract NNK to induce increased trypsin activity and pancreatic acinar damages.

Subtask 2. Test the hypothesis that PRSS1^{R122H} will sensitize the pancreas to ethanol and NNK-induced pancreatitis.

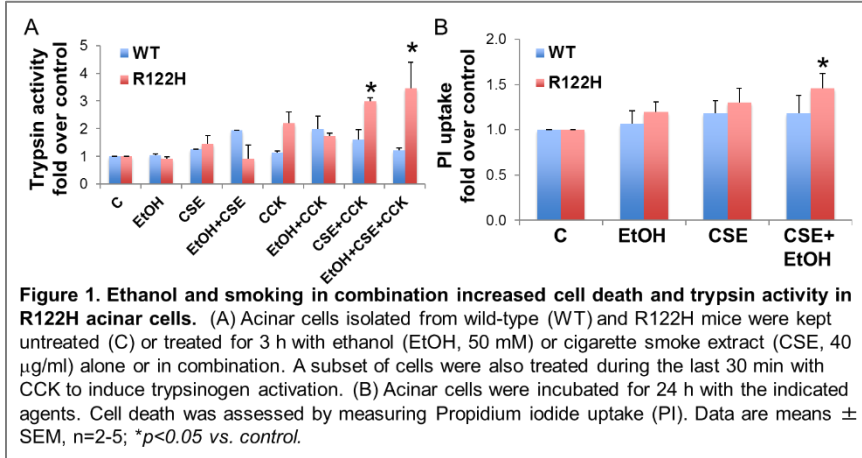
6.2. Accomplishments under the goals stated in the approved SOW

Subtask 1: Test the hypothesis that mutant PRSS1 expression cooperates with ethanol and smoke extract NNK to induce increased trypsin activity and pancreatic acinar damages. *Timeline, 18-36 months*

During the second funding Year, we continued working on the combined effects of ethanol and cigarette smoking extracts on the pathobiology of the pancreatic acinar cell. This work was included in our recent publication in Gastroenterology.¹ We reported that ethanol + a mixture of cigarette smoking compounds (CSE) promote acinar cell death in isolated mouse and rat acinar cells. Acinar cell death is associated with oxidative stress, ER stress and dysregulated ER stress responses. Moreover, CSE decreases levels of the UPR regulator and transcription factor XBP1. Reduction of XBP1 levels in acinar cells, by using XBP1 genetic deficient mice or XBP1 inhibitors, is associated with exacerbated ER stress, upregulation of cell death signaling, acinar cell damage, and loss of secretory capacity.^{1, 2} In addition, and in collaboration with Dr. Wilson and Dr. Apte (University of New South Wales, Australia), we studied whether smoking exacerbates pancreatitis responses in a rat model of alcoholic pancreatitis. In this model, pancreatitis manifests when alcohol feeding is accompanied by repeated administration of lipopolysaccharide (LPS), a bacterial product that promotes inflammation and can be elevated in the circulation of heavy drinkers due to increased gut permeability.³ The results of this study are included in our publication in Gastroenterology.¹ Briefly, we found that in the absence of LPS, ethanol feeding and smoking either alone or in combination induced minor pathological changes in pancreas. Similarly, LPS administration alone was insufficient to cause inflammation. However, ethanol feeding significantly induced pancreatic damage when co-administered with LPS and, notably, smoking further increased the severity of pancreatitis in alcohol-fed, LPS challenged rats. Thus, we observed increases in histologic scores for inflammatory cell infiltration, fibrosis, acinar cell vacuolization and cell death (necrosis + apoptosis). These histological changes were accompanied by ER stress and reduced number of digestive enzymes in acinar cells (evidenced by electron microscopy) and, importantly, dysregulation of adaptive ER stress responses. These

findings *in vivo* were similar to those found in cultured acinar cells treated with ethanol and smoking extracts. Taken together, the data indicates that our *in vivo* model recapitulates the acinar cell pathology and loss of adaptive cellular responses we observed in acinar cells in culture.^{1,2} However, it is important to note that in our *in vivo* model, ethanol feeding and smoking, (whether) alone or in combination decrease the threshold for pancreatitis, but by themselves are insufficient to induce acinar cell pathology. In this model, LPS administration is needed to initiate the inflammatory process that is further exacerbated by ethanol intake and smoking. Similar inflammatory input may be required in humans for initiation of pancreatitis since only a small percentage of heavy drinkers and smokers develop pancreatitis.

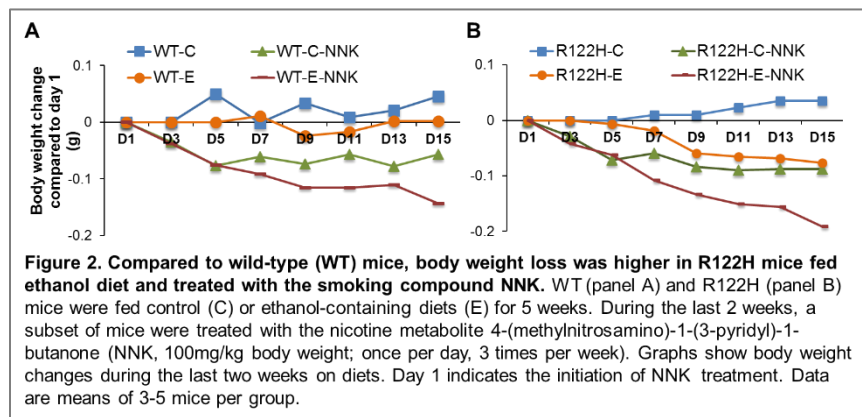
We next studied whether genetic mutations in the trypsinogen gene (PRSS1-R122H) sensitize the pancreas to ethanol and smoking-induced pancreatitis. We recently performed a systematic review of published literature and meta-analysis on the role of human PRSS1 p.R122H mutation in hereditary and non-hereditary chronic pancreatitis (CP); this report has been recently published in Gastroenterology Research Practice.⁴ We found that



of cholecystikinin, CCK; **Figure 1A**). Moreover, R122H acinar cells were more susceptible to death when treated with ethanol+CSE than wild-type cells (**Figure 1B**).

Subtasks 2: Test the hypothesis that PRSS1-R122H will sensitize the pancreas to ethanol and NNK-induced pancreatitis. Timeline, 1-24 months

We next performed *in vivo* studies to determine whether long-term ethanol feeding in combination with smoking induces pancreatitis in R122H mice. Seventeen wild-type (WT) and seventeen R122H mice were randomly allocated into two diet groups: the control diet group was fed a liquid Lieber-DeCarli control diet, and the ethanol diet group was fed a isocaloric liquid Lieber-DeCarli diet containing ethanol (36% of calories provided by ethanol). Mice were on diets for 5 consecutive weeks. During the last 2 weeks, a subset of mice was treated with the nicotine metabolite 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (**NNK**, 100 mg/kg body weight; once per day, 3 times per week), a tobacco-specific nitrosamine, and the rest of mice were treated with saline as



feeding alone (R122H-E group; **Figure 2B**) induced body weight loss in R122H mice, and this effect was significantly increased by administration of NNK (R122H-E-NNK group). These data indicate that R122H mice are more susceptible to the toxic effects of long-term ethanol feeding and smoking.

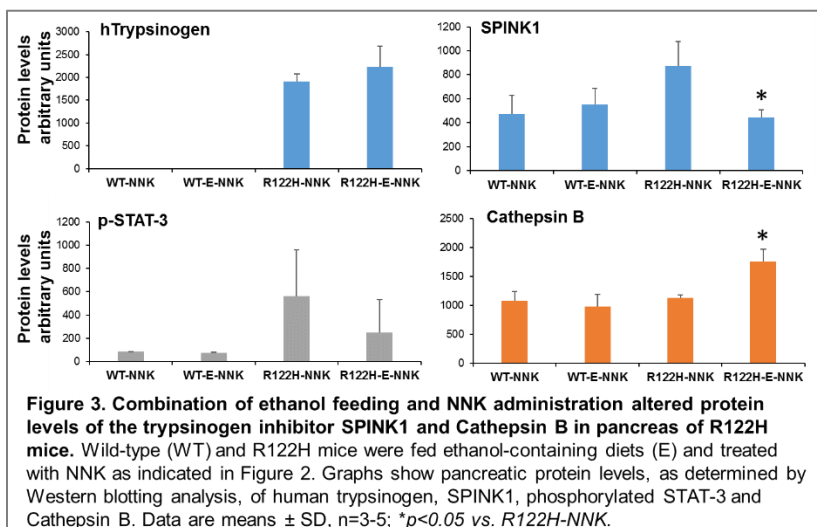


Figure 3. Combination of ethanol feeding and NNK administration altered protein levels of the trypsinogen inhibitor SPINK1 and Cathepsin B in pancreas of R122H mice. Wild-type (WT) and R122H mice were fed ethanol-containing diets (E) and treated with NNK as indicated in Figure 2. Graphs show pancreatic protein levels, as determined by Western blotting analysis, of human trypsinogen, SPINK1, phosphorylated STAT-3 and Cathepsin B. Data are means \pm SD, n=3-5; *p<0.05 vs. R122H-NNK.

We next examined whether ethanol and NNK treatments affect pancreatic protein levels of trypsinogen and its physiological inhibitor serine protease inhibitor Kazal-type 1 (SPINK1) in pancreas of WT and R122H mice. We also measured protein levels of Cathepsin B, a protease that promotes intracellular trypsinogen activation into trypsin during pancreatitis, and protein levels of STAT-3, a transcription factor that mediates cellular responses to inflammatory stimuli. As shown in **Figure 3**, R122H mice, but not WT mice, expressed the mutated form of human trypsinogen (htrypsinogen). Interestingly, levels of SPINK 1 were elevated in NNK-treated R122H, but significantly decreased

after ethanol+NNK treatments. Moreover, ethanol+NNK treatments led to significant upregulation of cathepsin B in R122H mice, an effect that together with the observed low levels of SPINK may sensitize these mice to pathological trypsinogen activation. We also found in these mice a mild increase in protein levels of phosphorylated STAT-3 suggesting activation of inflammatory pathways after ethanol feeding and NNK treatment. Despite these observed effects, ethanol feeding alone or in combination with NNK treatment induced only minor pancreas pathology in R122H or WT mice (not shown). These results are consistent with our previous study using rats,¹ indicating that inflammatory stimuli are required to unveil the toxic effects of ethanol feeding and smoking on pancreatic acinar cells.

To further characterize the effects of long-term ethanol feeding in R122H mice, we used a mouse model of alcoholic pancreatitis induced by low doses of cerulein (20 μ g/kg). Cerulein at these low doses has minor effects on pancreas of control-fed mice but induces an inflammatory reaction in ethanol-fed mice. As shown in **Figure 4A**, we found that ethanol feeding in the absence of cerulein treatment (R122H-saline group) did not induce histologic damage in pancreas of R122H mice. However, after cerulein treatment, pancreas displayed edema and inflammatory cell infiltration, effects that were exacerbated in ethanol-fed R122H compared to ethanol-fed WT mice. Consistent with these data, we found increased expression of inflammatory cytokines in pancreas of R122H mice compared to WT mice (**Figure 4**). In sum, our data support the concept that the p.R122H mutation predisposes to pancreatitis, and heavy drinking together with appropriate inflammatory stimuli may trigger a severe form of pancreatitis in individuals expressing this trypsinogen mutation.

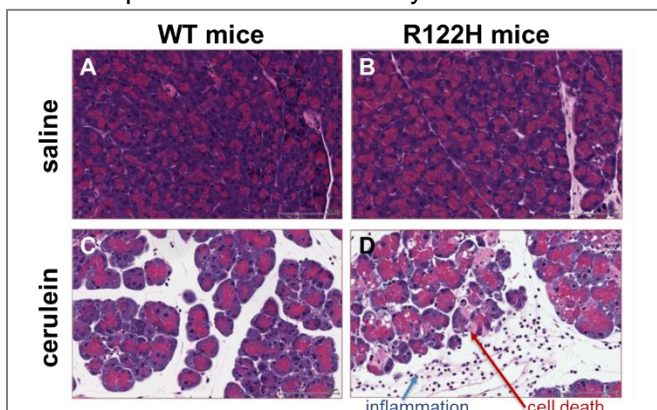


Figure 5. Pancreas of R122H mice display high numbers of infiltrating inflammatory cells and necrotic acinar cells during the acute phase of cerulein pancreatitis. 6-7 week-old mice were administered 7 hourly intraperitoneal injections of saline or 50 μ g/kg cerulein to induce acute pancreatitis. Tissues were collected 1 h after the last injection. Panels show H&E-stained pancreatic tissue sections; arrows indicate inflammatory cells infiltrating the pancreas and necrotic acinar cells.

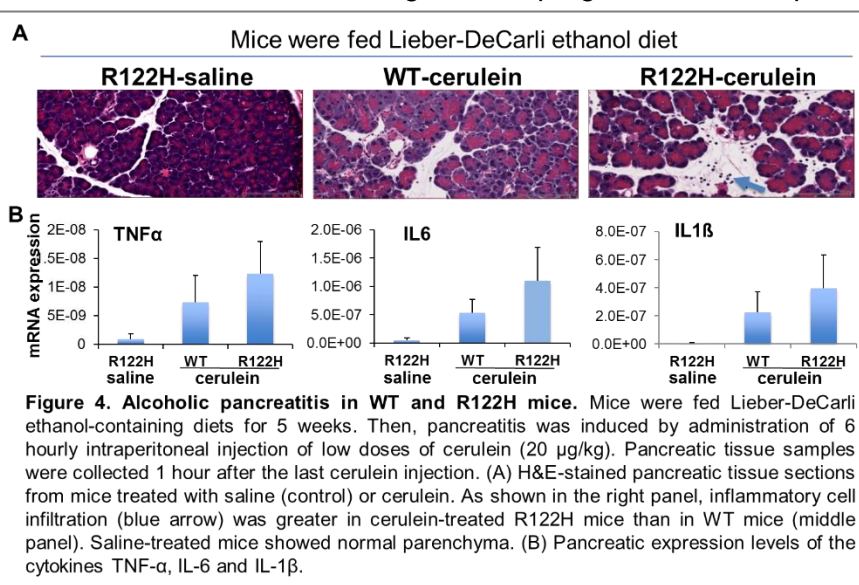


Figure 4. Alcoholic pancreatitis in WT and R122H mice. Mice were fed Lieber-DeCarli ethanol-containing diets for 5 weeks. Then, pancreatitis was induced by administration of 6 hourly intraperitoneal injection of low doses of cerulein (20 μ g/kg). Pancreatic tissue samples were collected 1 hour after the last cerulein injection. (A) H&E-stained pancreatic tissue sections from mice treated with saline (control) or cerulein. As shown in the right panel, inflammatory cell infiltration (blue arrow) was greater in cerulein-treated R122H mice than in WT mice (middle panel). Saline-treated mice showed normal parenchyma. (B) Pancreatic expression levels of the cytokines TNF- α , IL-6 and IL-1 β .

We next initiated studies to investigate in detail the effects of the pR122H mutation in acute and recurrent

pancreatitis, and whether the pR122H mutation predisposes to chronic pancreatitis. WT and R122H mice were subjected to one or two episodes of cerulein pancreatitis, and inflammatory responses were assessed during the acute phase of pancreatitis (1 h after the last cerulein injection) and during the recovery phase (2 days after the last cerulein injection). Pancreas tissue samples were analyzed to determine pancreatic edema and microscopic morphology, expression of the human trypsinogen mutation and pathological trypsin activity, acinar cell death and inflammatory signaling. **Figure 5** illustrates pancreas morphology at the acute phase of pancreatitis (one episode of pancreatitis). Both WT and R122H mice treated with saline control (Figure 5A-B) displayed a normal pancreatic parenchyma enriched in acinar cells organized in small acini. Cerulein administration induced in WT mice pancreatic edema, inflammatory cell infiltration and acinar cell damage (Figure 5C); and these effects were greatly augmented in R122H mice (Figure 5D). In particular, pancreas of R122H mice displayed extensive acinar cell necrosis and a dense

inflammatory cell infiltrate rich in neutrophils. In addition, we observed in cerulein-treated R122H mice a significant increase in intrapancreatic trypsin activity that was concomitant with a reduction in SPINK1 expression (**Figure 6A-B**). Moreover, pancreatic levels of inflammatory cytokines including TNF α , IL6 and IL1 β were higher during the acute phase of pancreatitis in R122H than in WT mice (**Figure 6C**).

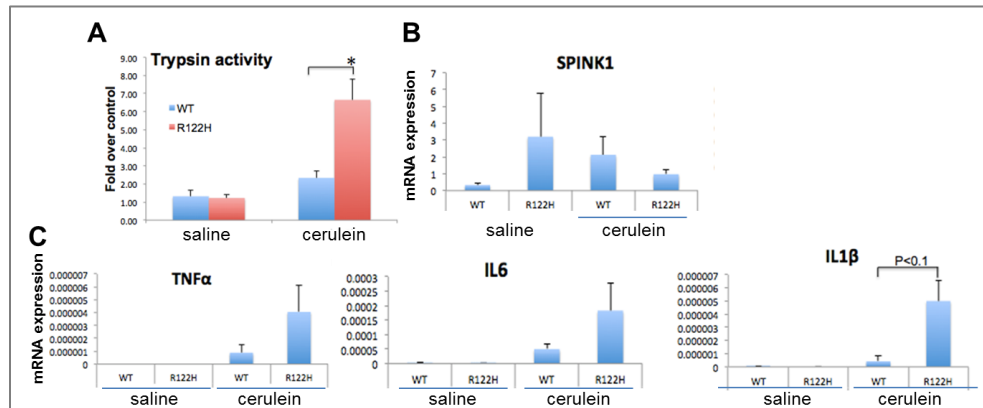


Figure 6. Trypsin activity and cytokine expression in pancreas of wild-type (WT) and R122H mice during the acute phase of cerulein pancreatitis. WT and R122H mice received 7 hourly intraperitoneal injections of saline or 50 μ g/kg cerulein to induce pancreatitis. Tissues were collected during the acute phase of pancreatitis (1 h after the last cerulein injection). (A) Compared to WT mice, cerulein-induced trypsin activity was significantly higher in R122H mice. However, mRNA levels of the trypsin inhibitor SPINK1 were lower in cerulein-treated R122H mice (B). (C) mRNA expression levels of TNF α , IL-6 and IL-1 β were higher in cerulein-treated R122H mice than in WT mice. Data are means \pm SD, n=3-5; * p <0.05.

inflammatory cell infiltrate rich in neutrophils. In addition, we observed in cerulein-treated R122H mice a significant increase in intrapancreatic trypsin activity that was concomitant with a reduction in SPINK1 expression (**Figure 6A-B**). Moreover, pancreatic levels of inflammatory cytokines including TNF α , IL6 and IL1 β were higher during the acute phase of pancreatitis in R122H than in WT mice (**Figure 6C**).

R122H mice subjected to recurrent episodes of cerulein pancreatitis displayed a severe form of pancreatitis during the acute phase (**Figure 7**). Trypsin activity increased in these mice by almost 10-fold over basal, compared to a 3-fold increase in WT mice, and pancreas of R122H mice exhibited an extensive inflammatory cell infiltrate rich in neutrophils and also monocytes/macrophages (not shown). In addition, we observed differentiation of acini into ductal structures (acinar-ductal-metaplasia), a phenomenon also observed in human chronic pancreatitis. Interestingly, pancreas recovery was impaired in R122H mice. As illustrated in **Figure 7B**, two days after cerulein administration the pancreatic parenchyma was greatly recovered in WT mice, although few inflammatory cells were still present in interlobular areas. However, pancreas of R122H mice still exhibited extensive inflammation, loss of acinar cells, poor acinar cell regeneration and ADM (Figure 7B-C). Moreover, expression levels of cytokines including IL6 and TNF α remained elevated during the recovery phase in R122H mice,

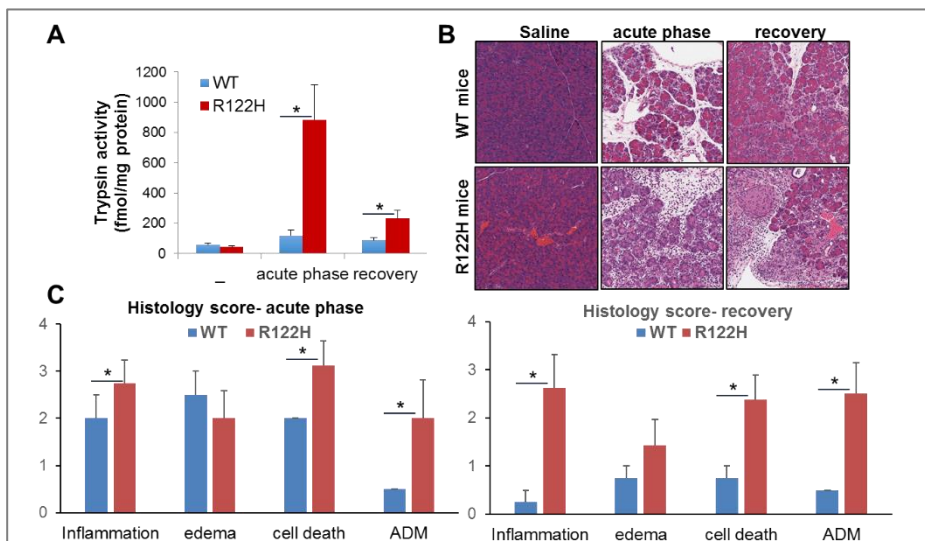
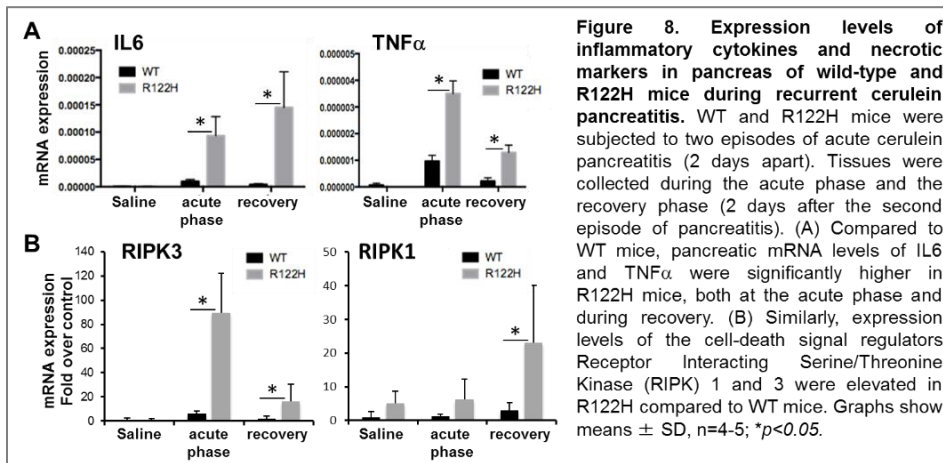


Figure 7. Pancreas damage in wild-type and R122H mice during recurrent cerulein pancreatitis. WT and R122H mice were subjected to two episodes of acute cerulein pancreatitis (2 days apart). Tissues were collected during the acute phase and the recovery phase (2 days after the second episode of pancreatitis). (A) Compared to WT mice, pancreatic trypsin activity was significantly higher in R122H mice both during the acute phase and during recovery. (B) H&E-stained pancreatic tissue sections from mice treated with saline (control) or cerulein (acute and recovery phases). As shown in the panels, pancreas recovery after cerulein-induced damage was markedly impaired in R122H mice. (C) H&E-stained pancreatic tissue sections were scored for inflammatory cell infiltration, edema, cell death, and acinar-ductal metaplasia (ADM). Graphs show means \pm SD, n=4-5; * p <0.05.

indicating unresolved inflammation (**Figure 8**). In these mice, we also found increased levels of the cell-death



signal regulators RIPK1 and RIPK3 during both the acute and the recovery phase of pancreatitis (**Figure 8B**).

Taking together, our data confirms our hypothesis that PRSS1-R122H sensitize the pancreas to alcoholic and non-alcoholic pancreatitis. During the next funding year we are planning to investigate the mechanisms underlying these sensitizing effects.

References

1. Lugea A, Gerloff A, Su HY, Xu Z, Go A, Hu C, French SW, Wilson JS, Apte MV, Waldron RT, Pandol SJ: Combination of Alcohol and Cigarette Smoke Induces Endoplasmic Reticulum Stress and Cell Death in Pancreatic Acinar Cells. *Gastroenterology* 2017.
2. Lugea A, Tischler D, Nguyen J, Gong J, Gukovsky I, French SW, Gorelick FS, Pandol SJ: Adaptive unfolded protein response attenuates alcohol-induced pancreatic damage. *Gastroenterology* 2011, 140:987-97.
3. Vonlaufen A, Xu Z, Daniel B, Kumar RK, Pirola R, Wilson J, Apte MV: Bacterial endotoxin: a trigger factor for alcoholic pancreatitis? Evidence from a novel, physiologically relevant animal model. *Gastroenterology* 2007, 133:1293-303.
4. Hu C, Wen L, Deng L, Zhang C, Lugea A, Su H-Y, Waldron RT, Pandol SJ, Xia Q: The differential role of human cationic trypsinogen (PRSS1) p.R122H mutation in hereditary and non-hereditary chronic pancreatitis: systematic review and meta-analysis. *Gastroenterol Res Pract* 2017, in press.

6.3. Opportunities for training and professional development

Nothing to report.

6.4. How were the results disseminated to communities of interest?

Results have been disseminated in laboratory meetings, the annual meeting of the American Gastroenterological Association (AGA), and in two publications (see section 9). Below are the abstracts presented in national meetings:

1. Hu C, Wen L, Deng L, Zhang C, Lugea A, Su H-Y, Waldron RT, Pandol SJ. The Differential Role of Human Cationic Trypsinogen (PRSS1) R122H Mutation in Hereditary and Non-Hereditary Chronic Pancreatitis: Systematic Review and Meta-Analysis. Digestive Disease Week, American Gastroenterological Association; Chicago, IL; May 7-9, 2017. Abstract published in: *Gastroenterology*, Vol. 152, Issue 5, S734.
2. Hu C, Su H-Y, Waldron RT, Xia Q, Ji B, Lugea A, Pandol SJ. Pancreatic acinar cells with human PRSS1R122H expression display higher susceptibility to stress induced by cholecystokinin or a combination of ethanol and cigarette smoke extracts. Digestive Disease Week, American Gastroenterological Association; Chicago, IL; May 7-9, 2017. Abstract published: *Gastroenterology*, Vol. 152, Issue 5, S899–S900.

6.5. Plans during the next reporting period to accomplish the goals

Plans detailed in the approved SOW for the next reporting period remain the same.

7. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report.

8. CHANGES/PROBLEMS:

Changes in approach and reasons for change

Nothing to report.

a. Actual or anticipated problems or delays and actions or plans to resolve them

Nothing to report.

b. Changes that had a significant impact on expenditures

Nothing to report.

c. Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

d. Significant changes in use or care of human subjects

Nothing to report.

e. Significant changes in use or care of vertebrate animals.

Nothing to report.

f. Significant changes in use of biohazards and/or select agents

Nothing to report.

9. PRODUCTS:

i. Journal publications.

1. Lugea A, Gerloff A, Su HY, Xu Z, Go A, Hu C, French SW, Wilson JS, Apte MV, Waldron RT, Pandol SJ: *Combination of Alcohol and Cigarette Smoke Induces Endoplasmic Reticulum Stress and Cell Death in Pancreatic Acinar Cells*. *Gastroenterology* 2017 Aug 25. pii: S0016-5085(17)36069-9. doi: 10.1053/j.gastro.2017.08.036. PMID:28847752

2. Hu C, Wen L, Deng L, Zhang C, Lugea A, Su H-Y, Waldron RT, Pandol SJ, Xia Q: The differential role of human cationic trypsinogen (PRSS1) p.R122H mutation in hereditary and non-hereditary chronic pancreatitis: systematic review and meta-analysis. *Gastroenterol Res Pract* 2017, *in press*. (**appendix 1**).

ii. Books or other non-periodical, one-time publications.

Nothing to report.

iii. Other publications, conference papers, and presentations.

Add abstracts to DDW as shown in *Gastroenterology*.

Website(s) or other Internet site(s)

Nothing to report.

Technologies or techniques

Nothing to report.

Inventions, patent applications, and/or licenses

Nothing to report.

Other Products

Nothing to report.

10. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

a. What individuals have worked on the project?

All individuals indicated as personnel in the project submission.

b. Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period? There is a new project funded:

Title: Statins prevent pancreatic diseases through mitophagy activation

Effort: 5% (PI, Pandol)

Supporting Agency: DoD (Discovery Award - W81XWH-16-PRMRP-DA)

Name & Address of Funding Agency/Grants Officer:

US Army Medical Research Acquisition Activity

FORT DETRICK – CDMRP, 1120 FORT DETRICK

FREDERICK MD 21702/Susan Dellinger

Performance Period: 05/01/2017 – 10/31/2018

Funding Amount: \$\$150,000 per year

Project Goals: This is study designed to determine the beneficial effects of statins involving pancreatic mitochondrial pathways.

Specific Aims: Specific aims

Aim 1. Determine the effects of simvastatin treatment in vitro and in vivo on expression of sXBP1 and pathways of mitophagy in acinar cells of the pancreas using human and murine acinar cells.

Aim 2. Determine the effect of the simvastatin treatments on Ca²⁺ signaling and mitochondrial responses to Ca²⁺ stress.

Aim 3. Determine the roles of HMG-CoA reductase and sXBP1 on the pathways of mitophagy, and mitochondrial and pancreatitis responses to Ca²⁺ stress

Overlap: There are no administrative, financial or scientific overlaps with the other previous, active or pending grant applications.

c. What other organizations were involved as partners?

Nothing to report.

11. SPECIAL REPORTING REQUIREMENTS

a. COLLABORATIVE AWARDS:

Nothing to report.

b. QUAD CHARTS:

Nothing to report.

12. APPENDICES:

Nothing to report.
